**In the claims:**

Please cancel claim 2.

Please amend claim 3 as follows:

B1 Exs and DD 1/9/06

3. (amended) A composition for treatment of advanced cutaneous T cell lymphoma in a human comprising recombinant interleukin-12 and an adjunct therapeutic agent which stimulates interferon-γ production, said adjunct therapeutic agent comprising a retinoid, interleukin 18, interferon-α or interferon-γ.

Please add new claim 4 as follows:

B2 4. A method for treatment of advanced cutaneous T cell lymphoma in a human comprising administering to a human an effective amount of recombinant interleukin-12 in a pharmaceutically acceptable carrier and an adjunct therapeutic agent which stimulates interferon-γ production.

**REMARKS**

Claims 1-3 remain in this application. Claim 2 has been canceled. Claim 3 has been amended. Claim 4 has been added to further clarify the invention, namely as a method for treatment

of advanced CTCL in a human comprising administering recombinant IL-12 in a pharmaceutically acceptable carrier with an adjunct therapeutic agent which stimulates interferon-γ production, as supported in the specification at page 8, lines 10-17. No new matter has been added by this amendment.

**I. Rejection of Claims 1-3 under 35 U.S.C. § 102(b)**

The Examiner has rejected claim 1 under 35 U.S.C. § 102(b) as being anticipated by Rook et al. (Clin. Exp. Immunol. 1997 January, 107 Suppl 1: 16-20). The Examiner has also rejected claim 3 under 35 U.S.C. § 102(a) as being anticipated by Lee et al. (Leukemia and Lymphoma, 1998 May 29(5-6) 427-38).

The Examiner has suggested that Rook et al. disclose clinical trials of recombinant IL-12 for treatment of cutaneous T cell lymphoma wherein IL-12 is administered subcutaneously. Applicant respectfully disagrees with the Examiner's characterization of this reference.

A general level of operability is required in a reference to establish a *prima facie* case of obviousness or anticipation. See MPEP § 2121. In accordance with MPEP § 2121.01, the test in determining that quantum of prior art disclosure which is

necessary to declare an applicant's invention "not novel" or "anticipated" within section 102, is whether a reference contains an "enabling disclosure". *In re Hoeksema*, 399 F.2d 269(CCPA 1968). A reference contains an "enabling disclosure" if the public was in possession of the claimed invention before the date of invention. Rook et al. do not teach treatment in humans, it was not until after the publication at issue that the clinical efficacy of IL-12 in CTCL patients was discovered, see attached Declaration by inventor. Further, since Rook et al. do not teach administering compositions comprising either the pharmaceutical carrier nor adjunct therapeutic agents, this reference cannot anticipate new claim 4.

Withdrawal of this rejection is respectfully requested.

The Examiner has further rejected claim 3 as being anticipated by Lee et al. The Examiner suggests that Lee et al. teach a composition comprising recombinant IL-12 and IL-15, and the effects of the combination of the IL-12 and IL-15 with regard to anti-tumor immunity. In an earnest effort to advance the prosecution of this case, claim 3 has been amended to delete IL-15 from the claimed adjunct therapeutic agents. Withdrawal of this rejection is respectfully requested in light of the amendment to claim 3.

**II. Rejection of Claims 1-3 under 35 U.S.C. § 103**

The Examiner has rejected claims 1-3 under 35 U.S.C. § 103(a) as being unpatentable over Rook et al. (Ann. NY Acad, 1996, 795:310-318) in view of Verbik et al. (Clin. Exp. Metastasis, 1996, 14:219-229). The Examiner has further rejected claim 3 as being unpatentable over Rook et al. and Verbik et al. as applied to claims 1-3 and further in view of Osaki et al. and Rook et al. (Clin. Exp. Immunol., 1997, 107 Suppl. 1:16-20).

The Examiner suggests that Rook et al. (1996) demonstrate that depressed IFN-γ production is normalized *in vitro*, indicating that a marked defect in IL-12 production by SzS PBMC's may be an important factor in the failure of producing normal amounts of IFN-γ and mediating normal cell-mediated immunity. The Examiner has acknowledged that Rook et al. do not teach a method for *in vivo* treatment. The Examiner further suggests that Verbik et al. teach a method for treatment of a murine lymphoma with IL-12 in mice. Applicant respectfully traverses this rejection.

To establish a *prima facie* case of obviousness under 35 U.S.C. 103(a) three basic criteria must be met. MPEP § 2143. First, there must be some suggestion or motivation, either in the

references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all of the claim limitations.

The cited combination of prior art references fails to meet all of these criteria with respect to the instant claimed invention.

The Examiner has rejected claim 1, suggesting that it would have been obvious to a person of ordinary skill in the art at the time the invention was made to design a method of treatment of advanced CTCL in a human by administering IL-12 based upon the teachings of Rook et al. (Referencing IL-12 deficiency and normalization of IFN-γ by exogenous IL-12 in SzS PBMCs). The Examiner suggests that one skilled in the art would be motivated to do so as Verbik et al. teach strongly toward an expectation of success *in vivo*.

The Examiner has rejected claim 2, suggesting that it would have been obvious to the person of ordinary skill in the art at the time the invention was made to design a method as claimed for treatment of advanced CTCL in a human by administering recombinant IL-12 with an adjunct therapeutic agent stimulating

IFN-γ production, based upon strong indications taught by Rook et al., as IFN-γ is a Th1 cytokine. The Examiner suggests that one of skill would be motivated to do so at Rook's suggestion and would have expected success because both IL-12 and IFN-γ share the same function towards stimulating IFN-γ production. Applicant respectfully disagrees with the rejections of claims 1 and 2.

Neither of the cited prior art references provide one of skill in the art with a reasonable expectation of successfully treating advanced cutaneous T cell lymphoma in a human via administration of IL-12 alone or in combination with an adjunct therapeutic agent which stimulates interferon-γ production.

As acknowledged by the Examiner, Rook et al. (1996) teach *in vitro* culture experiments with PBMCs and the single cytokine IL-12. Rook et al. (1996) do not teach a method for *in vivo* treatment.

Verbik et al. teach administration of IL-12 to mice suffering from liver lymphoma. Even as such, the use of IL-12 with other interleukins caused unexplained early deaths in test mice. As is taught on page 227 of the reference, the IL-12 is believed to have induced secretion of IFN-γ causing gastrointestinal damage to the tissue of the mice resulting in

their death. Further, mice undergoing radiation after administration of IL-12 suffered severe gastrointestinal damage which was much more pronounced than damage induced by radiation alone, page 227, column 2. Verbik et al. further teach that the mechanisms through which the IL-12 mediates *in vivo* anti-tumor responses is not fully understood.

As discussed in detail in the instant application at pages 5 and 6, cytokine pathways are extremely complex and exhibit cross-regulation, where the cytokines secreted by one subset of Th cells can block production and activity of cytokines secreted by the other subset. Accordingly, the success of administration of a single cytokine *in vivo* to a patient suffering from advanced cutaneous T cell lymphoma can not reasonably be predicted based upon *in vitro* experiments such as described by Rook et al. (1996). Further, the teachings of Verbik suggest that administration of IL-12 *in vivo* may cause severe gastrointestinal tissue damage due to increased levels of IFN-γ, leading to death in the subject, page 227. As the Examiner has indicated, Verbik et al. do not teach therapeutic application of IL-12 in humans or in connection with CTCL. Thus, one skilled in the art would not be motivated to administer IL-12 to a human with any expectation of success. On the contrary, a skilled person would refrain from

administering interleukin-12, alone or in combination with other interleukins to a human based upon the teachings of Rook et al. (1996) and Verbik et al.

Withdrawal of these rejections is respectfully requested.

The Examiner has further rejected claim 3, suggesting that it would have been obvious to a person of skill in the art at the time of the invention to make a composition comprising a recombinant IL-12 and IFN-γ or a retinoid in order to practice the method for treatment of advanced CTCL as set forth in claim 3. The Examiner further suggests that one of ordinary skill in the art would have been motivated for the same reasons addressed in the Examiner's claim 2 rejection, *supra*. Applicant respectfully disagrees.

As set forth *supra*, the cytokine pathways are extremely complex and exhibit cross-regulation. *In vitro* models could not possibly predict the effect of *in vivo* treatment in a human. Further, Verbik et al. teach that administration of IL-12 is believed to induce secretion of IL-γ causing gastrointestinal damage to test mice, resulting in early death. Thus, there would be no motivation to administer **both** IL-12 and IL-γ or IL-12 and retinoids (which increase IL-γ production) to a human. Nor

would there be a reasonable expectation of success of the administration of IL-12 in combination with IL-γ or a retinoid given the complex cytokine regulation pathways.

The Examiner has further rejected claim 3 under 35 U.S.C. § 103(a)as being unpatentable over Rook et al. (1996) and Verbik et al. as applied to claims 1-3 above, and further in view of Osaki et al. (Journal Immunol. 1998 February, 160:1742-49) and Rook et al. (Clin. Exp. Immunol., 1997, 107 Suppl. 1:16-20). Applicant respectfully disagrees.

As discussed *supra*, Rook et al.(1996) teach *in vitro* culture experiments with PBMCs and the single cytokine IL-12. Rook et al.(1996) do not teach a composition comprising recombinant IL-12 with IL-18 or IFN-α.

As discussed *supra*, Verbik teaches away from treatment by a composition of both IL-12 and adjunct therapeutic agents which stimulate the production of INF-γ, see page 227. As it is suggested to have caused death in some test mice. Further, it teaches that lethally irradiated mice treated with IL-12 had severe gastrointestinal damage which was much more pronounced that damage that was induced by radiation alone, page 227.

Osaki teaches the use of IL-18 and IL-12 in specific mice. Osaki further teaches that although combination treatment with

IL-18 and IL-12 markedly suppressed tumor growth in mice, all of the mice treated with the IL-12 and IL-18 combination died prior to the completion of the treatment, see page 1743, column 2. Later tested mice became so ill with treatment of the combination of IL-12 and IL-18 that the treatment was discontinued after the fourth injection, see page 1744, column 1.

Rook et al. (1997) teach that the PMBCs of CTCL patients exhibit an increased production of T-helper type 2 cytokines (IL-4 and IL-5) and deficient Th1 cytokines (IL-2 and IFN-α). Rook et al.(1997) teach *in vitro* culture experiments with IL-12 and suggests that IL-12 and IFN-α may suppress the growth of CD4T cells *in vitro*.

As acknowledged by the Examiner, Rook et al. (1996) do not teach a composition comprising a recombinant IL-12 and IL-18 or IFN-α. Osaki et al. teach a defective composition of IL-12 and IL-18 in that all of the test subjects administered the composition either died or became so sick that the doses of the composition had to be ceased. A skilled person would not have any reasonable expectation of success in treatment of humans with the IL-12/IL-18 combination based upon the teachings of Osaki. Further, the teachings of Osaki would motivate a skilled person

to refrain from treatment of human subjects with IL-12 and IL-18 given the adverse effects.

In addition, Rook et al.(1997) do not teach administration of IL-12 or IL-12 with any other component to a human. While Rook et al. (1997) suggest that growth of CD4+ cells was significantly suppressed by IL-12 and IFN-α *in vitro*, there is no indication that this combination would be successful in humans. Especially in light of Verbik et al. where *in vivo* application of IL-12 resulted in severe gastrointestinal damage and is suspected to have caused early death in the animals. Further, a skilled person would not be motivated to administer a IL-12/IL-18 combination to a human in light of the Osaki teachings, showing death or excessive illness due to IL-12 and IL-18 in test animals. Nor would a skilled person expect success in the administration of IL-12 and IFN-α, given the complex and unpredictable cytokine pathways.

MPEP § 2143 and the Courts are quite clear; both the teaching or suggestion to make the claimed combination and the reasonable expectation of success must be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). The cited combination of prior art fails to provide this reasonable expectation of

success. It is only with the instant specification in hand, which demonstrates the efficacy of Applicant's invention that one of skill has a reasonable expectation of success.

Accordingly, this combination of cited prior art does not render the instant claimed invention *prima facie* obvious. Withdrawal of this rejection under 35 U.S.C. § 103 is therefore respectfully requested.

**III. Conclusion**

Applicant believes that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment, captioned "Version with

Markings to Show Changes Made". Also attached is a Declaration by the Inventor.

Respectfully submitted,

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Date: **August 3, 2001**

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**VERSION WITH MARKINGS TO SHOW CHANGES MADE**

**In the claims:**

Claim 2 has been canceled.

Claim 3 has been amended as follows:

3. (amended) A composition for treatment of advanced cutaneous T cell lymphoma in a human comprising recombinant interleukin-12 and an adjunct therapeutic agent which stimulates interferon-γ production, said adjunct therapeutic agent comprising a retinoid, ~~interleukin 15~~, interleukin 18, interferon-α or interferon-γ.